(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 April 2006 (06.04.2006)

PCT

(10) International Publication Number
WO 2006/035416 A2

(51) International Patent Classification:
*A61K 9/50* (2006.01) *A61K 31/4422* (2006.01)

(21) International Application Number:
PCT/IE2005/000104

(22) International Filing Date:
27 September 2005 (27.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

| | | |
|---|---|---|
| 60/612,784 | 27 September 2004 (27.09.2004) | US |
| 60/612,785 | 27 September 2004 (27.09.2004) | US |
| 60/612,786 | 27 September 2004 (27.09.2004) | US |

(71) Applicant *(for all designated States except US)*: **SIGMOID BIOTECHNOLOGIES LIMITED** [IE/IE]; 62 Merrion Square, Dublin 2 (IE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MOODLEY, Joey** [IE/IE]; Rindoon, Retreat Road, Athlone, County Westmeath (IE). **COULTER, Ivan** [IE/IE]; 21 Leeson Street, Dublin 2 (IE).

(74) Agents: **O'Brien, John, A.** et al.; John A. O'Brien & Associates, Third Floor, Duncairn House, 14 Carysfort Avenue, Blackrock, County Dublin (IE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *without international search report and to be republished upon receipt of that report*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2006/035416 A2

(54) Title: MINICAPSULE FORMULATIONS

(57) Abstract: A formulation comprises a plurality of seamless minicapsules, the minicapsules having a diameter of from 0.5 mm to 5 mm, the minicapsules having a core containing an active entity and an encapsulating body, the active entity being in the form of any one or more of: a microemulsion, a nanoemulsion, a self-emulsifying delivery system, a self-microemulsifying delivery system, a biostable perflurocarbon formulation, a complex with cyclodextrin (and the like), liposomes, hydrogel, lymphatic targeted delivery system, liquid bi-layers, an aqueous System, wax, emzaloid, and natural plant extract.

# "Minicapsule Formulations"

## Field of the Invention

The present invention relates to formulations utilising seamless minicapsule or minispheres, to enhance the formulation of and bioavailability of pharmaceutical and nutritional actives, including small molecules, biopharmaceuticals, veterinary actives, vaccines, immunotherapeutics, biotechnicals and nutritionals which are intended for oral, rectal, vaginal, intrauterine, nasal or pulmonary administration.

The advantages of controlled/sustained/pulsatile pharmaceutical or nutritional administration are well known. They ensure that better disease management through controlling the concentration of active that is present in the intestine or plasma at any time to that required for optimal therapeutic or nutritional benefit. Controlled release ensures both that the concentration is neither at a low sub-therapeutic nor a high toxic level. Also, pulsatile release format mimics the administration of drugs at different time points without the need for several administrations. Controlled release reduces irritation to the gastrointestinal membranes.

This invention is directed towards providing minicapsule formulations of ingredients which have heretofore proved very difficult to formulate.

## Statements of Invention

According to the invention there is provided a formulation comprising a plurality of seamless minicapsules, having a diameter of from 0.5 mm to 5 mm the minicapsules having a core containing an active entity and an encapsulating body, the active entity being in the form of any one or more of:-

a microemulsion,

a nanoemulsion,

a self-emulsifying delivery system,
a self-microemulsifying delivery system,
a biostable perflurocarbon formulation,
a complex with cyclodextrin (and the like),
liposomes,
hydrogel,
lymphatic targeted delivery system,
liquid bi-layers,
wax,
an aqueous system,
emzaloid,
a natural plant extract.

In one embodiment at least some of the minicapsules have at least one coating to control the time and/or location of the release of the active entity.

The coated seamless minicapsules may have a diameter of from 0.5 mm to 5.0 mm, from 1.2 mm to 2.0 mm, 1.4 mm to 1.8 mm.

In one embodiment at least one coating is an immediate release coating. At least one coating may be a sustained release coating. The coating may comprise a sustained release and an immediate release coating. At least one coating may be an enteric coating. At least one coating may be a bioadhesive coating. The bioadhesive coating may be a mucoadhesive coating.

In one embodiment the minicapsule comprises a buffer layer.

The minicapsule may be formed from a core solution containing an active ingredient, and an encapsulating solution which forms, on setting, the encapsulating medium. The encapsulating solution may contain an active ingredient. The active ingredient contained in the encapsulating solution may be

the same as the active ingredient in the core solution. Alternatively the active ingredient contained in the encapsulating solution is different from the active ingredient in the core solution. The active ingredient contained in the encapsulating solution may be in a micronised or nanonized particle form.

In one embodiment the minicapsule is formed from a solution containing the encapsulating medium and an active ingredient.

In one case the active ingredient contained in the encapsulating solution is in a micronised or nanonized particle form.

In one embodiment the formulation comprises at least two different populations of minicapsules. One population of minicapsules may comprise minicapsules with one rate-controlling coating and another population of minicapsules comprises minicapsules with a second rate-controlling coating. One population of minicapsules may have an immediate release coating and the other population of minicapsules has a sustained or controlled release coating. One population of minicapsules may not have a coating. Alternatively or additionally one population of minicapsules contains a first active ingredient and another population of minicapsules contains a second active ingredient.

In one respect the formulation comprises a capsule containing a plurality of minicapsules. The capsule may contain another entity. The other entity may be in a liquid, powder, solid, semi-solid or gaseous form. The other entity may comprise an active entity.

In another aspect a formulation comprises a tablet or pellet containing a plurality of minicapsules. The tablet or pellet may contain another entity. The other entity may be an active entity.

In another aspect there is provided a formulation comprising a plurality of seamless minicapsules, the minicapsules having:-

(i) a core containing an active entity, the active entity being

- solubilised in an acceptable solvent,
- in a liquid phase,
- in a solid form, and/or
- in a semi-solid form

and

(ii) an encapsulating medium (body)

- the seamless minicapsules having a diameter of from 0.5mm to 5.0mm.

In another aspect the invention provides a formulation comprising a plurality of seamless minicapsules, the minicapsules containing an active entity in a solid and/or semi-solid form and an encapsulating medium, the seamless minicapsules having a diameter of from 0.5 mm to 5 mm. In the invention a the powder/solid material is initially dissolved/suspended in a liquid phase (e.g. gelatin). On cooling/hardening of the liquid phase, the solid material comes out of solution and is present as a solid in the hardened core. This type of formulation would generally comprise of a non-layered gelatin microcapsule core coated with an appropriate polymer. Such a formulation would be suitable for nanoparticle formulations.

- Nanoparticles (particles less than 800nm in size that are said to be taken up intact from the GIT) could be formulated as a solid core by initially dissolving the particles in gelatin before cooling (as described above).

- PEG- coated nanoparticles – solid core formulated in a similar manner to that of the nanoparticles. PEG-coated nanoparticles are capable of targeting specific tumours.

At least some of the minicapsules may have at least one coating to control the time and/or location of the release of the active entity. The coated seamless minicapsules have a diameter of from 0.5 mm to 5.0 mm, 1.2 mm to 2.0 mm, 1.4 mm to 1.8 mm.

In one embodiment at least one coating is an immediate release coating and/or a sustained release coating, and/or a sustained release and an immediate release coating, and/or an enteric coating and/or a bioadhesive coating such as a mucoadhesive coating.

In one embodiment at least some of the minicapsules comprises a buffer layer.

In one arrangement the minicapsule is formed from a core solution containing an active ingredient, and an encapsulating solution which forms, on setting, the encapsulating medium. The encapsulating solution may contain an active ingredient. The active ingredient contained in the encapsulating solution may be the same as or different from the active ingredient in the core solution. The active ingredient contained in the encapsulating solution may be in a micronised or nanonized particle form.

In another embodiment the minicapsule is formed form a solution containing the encapsulating medium and an active ingredient. The active ingredient contained in the encapsulating solution is in a micronised or nanonized particle form.

In one embodiment the formulation comprises at least two different populations of minicapsules. One population of minicapsules may comprise minicapsules

with one rate-controlling coating and another population of minicapsules comprises minicapsules with a second rate-controlling coating. One population of minicapsules may have an immediate release coating and the other population of minicapsules has a sustained or controlled release coating. One population of minicapsules may not have a coating. One population of minicapsules may contain a first active ingredient and another population of minicapsules may contain a second active ingredient.

In one aspect the formulation comprises a capsule containing a plurality of minicapsules. The capsule may contain another entity. The other entity may be in a liquid, powder, solid, semi-solid or gaseous form. The other entity may comprise an active entity.

In another embodiment the formulation comprises a tablet or pellet containing a plurality of minicapsules. The tablet or pellet may contain another entity. The other entity may be an active entity.

The invention further provides a formulation comprising a plurality of seamless minicapsules, at least some of the minicapsules comprising a plurality of particles containing an active entity dispersed in an encapsulating body, the seamless minicapsules having a diameter of from 0.5 mm to 5 mm. At least some of the minicapsules have at least one coating to control the time and/or location of the release of the active entity. The coated seamless minicapsules have a diameter of from 0.5 mm to 5.0 mm, from 1.2 mm to 2.0 mm, from 1.4 mm to 1.8 mm.

At least one coating may be an immediate release coating, and/or a sustained release coating, and/or a sustained release and an immediate release coating, and/or an enteric coating, and/or a bioadhesive coating such as a mucoadhesive coating.

The minicapsule may be formed from a solution containing the encapsulating medium and an active ingredient. The active ingredient contained in the encapsulating medium may be in a micronised or nanonized particle form.

The formulation may comprise at least two different populations of minicapsules. One population of minicapsules may comprise minicapsules with one rate-controlling coating and another population of minicapsules comprises minicapsules with a second rate-controlling coating. One population of minicapsules may have an immediate release coating and the other population of minicapsules has a sustained or controlled release coating. One population may not have any rate-controlling coating. One population of minicapsules may contain a first active ingredient and another population of minicapsules may contain a second active ingredient.

The formulation may comprise a capsule containing a plurality of minicapsules. The capsule may contain another entity. The other entity may be in a liquid, powder, solid, semi-solid or gaseous form. The other entity may comprise an active entity.

The formulation may comprise a tablet or pellet containing a plurality of minicapsules. The tablet or pellet may contain another entity. The other entity may be an active entity.

The invention also provides a formulation comprising a plurality of seamless minicapsules having at least two populations selected from:-

a first minicapsule population in which the minicapsules comprise a core containing an active ingredient and an encapsulating medium, the minicapsules having a diameter of from 0.5 mm to 5 mm;

a second minicapsule population in which the minicapsules comprise a plurality of particles containing an active entity dispersed in an encapsulating medium, the minicapsules having a diameter of from 0.5 mm to 5 mm; and

a third micro or mini particles population in which the minicapsules comprise an inert core and at least one layer around the core, the layer containing an active ingredient.

In one embodiment of the various aspects of the invention at least some of the minicapsules are provided with a bioadhesive such as a mucoadhesive.

The bioadhesive may comprise from 0% to 10% by weight of one or more of the following polymer classes:- polyacrylates; polyanhydrides; chitosans; carbopols; cellulose; methylcellulose; methylated deoxycellulose (m-doc™), lectins.

The bioadhesive may comprise from 0% to 10% by weight of one or more of the following thiolated or otherwise derivatised polymers:- polyacrylates; polyanhydrides; chitosans; carbopols; cellulose; methylcellulose; methylated deoxycellulose (m-doc™), lectins.

The bioadhesive may comprise a coating. Alternatively or additionally the bioadhesive is incorporated into a part or layer of the minicapsule such as into the rate-controlling layer and/or into the encapsulating medium.

In another embodiment at least some of the minicapsules have a layer such as an outer layer which is divided into at least two parts. The parts may be of the same or different composition.